I. AMENDMENTS

Please amend the subject application as follows:

In the claims:

Please amend claim 15 to recite as follows:

A1

15. (Amended) A method for treating or preventing a disorder associated with estrogen deficiency or disregulation in a subject comprising contacting an application situs of the subject with an effective pharmaceutical formulation of claim 1.

II. REMARKS

Claims 1 to 19 are pending in the application. By this Amendment, claim 15 has been amended. Accordingly, claims 1 through 14, 16 through 19 and amended claim 15 are presently under examination.

Claim 15 has been amended to correct a typographical error. The word "disdregulation" has been amended to "disregulation". Support for this amendment is found specifically at page 11, lines 8 to 10. An issue of new matter is not raised by this amendment and entry thereof is respectfully requested.

Attached hereto is a marked-up version of the changes made to claim 15 by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

In view of the preceding amendment and the following remarks, Applicants respectfully request reconsideration and withdrawal of the outstanding objections and rejections.

Claim Objections

Claim 15 stands objected to because of misspelling "disregulation." Applicants have amended claim 15 to correct this inadvertent, typographical error. In view of the amendment to claim 15, Applicants respectfully request reconsideration and withdrawal of the objection to claim 15.

35 U.S.C. §103

Claims 1 through 6, 8 through 12 and 15 through 17 stand rejected under 35 U.S.C. §103 (a) as allegedly unpatentable over Jain, et al. (U.S. Patent No. 5,780,050) in view of Patchett, et al. (U.S. Patent No. 6,043,026) and Ke, et al. (*Endocrinology* **139** (4): 2068-2076 (1998)).

The Office alleged that Jain, et al. discloses a transdermal formulation comprising a liquid drug reservoir, an adhesive solvent/water based pressure sensitive matrix and a permeation enhancer. The Office also alleged that Jain, et al. discloses the formulation to comprise ethanol and glycerol monooleate as possible solvents and penetration enhancers. The Office also further alleged that Jain, et al. discloses the use of sex hormones as the active ingredient to influence various physiological functions, for example.

The Office alleged that Patchett, et al. discloses a combination therapy for the prevention and treatment of osteoporosis comprised of a compound containing estrogen receptor modulators, one of which allegedly may be lasofoxifene (also known as CP-336156). The Office also alleged that Patchett, et al. suggests that the compound above can be formulated into a topical solution and that this topical solution can be formulated into a transdermal solution. The Office further alleged that Ke, et al. discloses that lasofoxifene can be used as an estrogen steroid substitute in hormone replacement therapy.

The Office argued that one of ordinary skill in the art would have been motivated to combine the compound of Patchett, et al. with the transdermal formulation of Jain, et al. in order to impart estrogen-agonistic/antagonistic properties on the formulation. The Office further argued that it would have been obvious to one of ordinary skill in the art to combine these disclosures to obtain the allegedly expected result of a transdermal formulation useful in the treatment of estrogen deficient disorders. Applicants respectfully traverse.

Claim 1 recites a transdermal formulation comprising a drug reservoir and an effective amount of lasofoxifene and the pharmaceutically acceptable salts thereof. Claim 2 depends from claim 1 and further comprises a drug permeation enhancer. Claim 3 recites a transdermal formulation comprising an adhesive drug matrix reservoir and an effective amount of lasofoxifene and the pharmaceutically acceptable salts thereof. Claims 4 and 5 depend from

claim 3 and provide that the adhesive drug matrix is either solvent based or water based pressure sensitive. Claim 6 recites a transdermal formulation comprising a liquid reservoir drug reservoir and an effective amount of lasofoxifene and the pharmaceutically acceptable salts thereof. Claims 8 through 12 are drawn to the formulations of claims 3 through 8 and further comprise a drug permeation enhancer, which comprises a lower alkanol and an effective amount of glycerol monooleate. Claims 15 through 17 recite a method for treating disorders associated with estrogen deficiency or disregulation with the formulations of any of claims 1 through 7.

Jain, et al. teaches a stabilized patch device for transdermal drug delivery of steroid drugs which contain a 3-keto-4-en functional group. *See* abstract; column 1, lines 12 through 14; claim 2.

Patchett, et al. discloses a composition comprised of two separate active ingredients: 1) an estrogen receptor modulator and 2) a growth hormone secretatogogue for use in the treatment or prevention of diseases involving bone resorption. *See* Abstract and claim 1.

Ke, et al. merely states that lasofoxifene is also known as CP-336156.

In contrast, Applicants' invention is a transdermal delivery system containing lasofoxifene. *See* claims 1-19 and throughout the specification. Lasofoxifene is not a drug (sex hormone or steroid drug) containing a 3-keto-4-en functional group, as taught by Jain, et al. Accordingly, one of skill in the art would not be lead to combine the teachings of Patchett, et al. to Jain, et al., since there is no indication in the cited art that lasofoxifene is capable of effective transdermal delivery. Additionally, the combination of Jain, et al., in view of Patchett, et al. and Ke, et al. would not lead one of skill in the art to a patch device for transdermal drug delivery of a drug lacking the 3-keto-4-en functional group. Moreover, given the different chemical properties of the active agents of the cited art, there is no expectation of success.

The Federal District Court has stated that "[o]ur case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *In re Dembiczak*, 175 F.33 994, 999 (Fed. Cir. 1999). In order to show that there existed a showing of motivation to combine the references, "the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no

knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998).

Therefore, the cited art does not teach the combination as suggested by the Office and claims 1 through 6, 8 through 12 and 15 through 17 are not rendered obvious in light of the abovementioned references.

Claims 7 and 13 stand rejected under 35 U.S.C. §103 (a) as allegedly unpatentable over Venkateshwaran, et al. (U.S. Patent No. 5,912,009) in view of Patchett, et al. (U.S. Patent No. 6,043,026) and Ke, et al. (*Endocrinology* **139** (4): 2068-2076 (1998)).

The Office opined that Venkateshwaran, et al. teaches a transdermal formulation where a hydroalcoholic gel is created comprising glycerin, water, enhancer and a drug. The Office also agrued that this reference teaches a method of application of the invention, whereby the invention is brought into contact with the skin and is held in place by a type of adhesive, allegedly bringing the reservoir into contact with the skin and allowing diffusion through the skin. The Office further admitted that while Venkateshwaran, et al. does not teach the inclusion of lasofoxifene in the formulation, but that Venkateshwaran, et al. suggests that the drug can be any number of compounds suitable for topical and transdermal administration including hormones.

The Office alleged that Patchett, et al. discloses a combination therapy for the prevention and treatment of osteoporosis comprised of a compound containing estrogen receptor modulators, one of which allegedly may be lasofoxifene (also known as CP-336156). Patchett, et al. was cited for allegedly teaching that the compound above can be formulated into a topical solution and that this topical solution can be formulated into a transdermal solution. The Office further opined that Ke, et al. disclose that lasofoxifene can be used as an estrogen steroid substitute in hormone replacement therapy.

In the Office's opinion it therefore would have been obvious to one of ordinary skill in the art to combine the teachings of Venkteshwaran, et al. with the compound of Patchett, et al. in order to impart estrogen-agonistic/antagonistic properties on the formulation. Additionally, the Office alleged that it would have been obvious to one of ordinary skill in the art to combine these

disclosures to obtain the allegedly expected result of a transdermal formulation useful in the treatment of estrogen deficiency disorders. Applicants respectfully traverse.

Claim 7 recites a transdermal formulation comprising a free form hydroalcoholic gel and an effective amount of lasofoxifene and the pharmaceutically acceptable salts thereof. Claim 13 recites a transdermal devise which comprises a means for adhering the drug reservoir to the application situs and the pharmaceutical formulations of any of claims 3 to 7.

Jain, et al., Patchett, et al. and Ke, et al. teach as noted above by Applicants. The combination of these references fail to teach or suggest the claimed invention. Venkteshwaran, et al. fails to shore up the deficiencies present in the prior combination. Claims 7 and 13 are not rendered obvious in light of the abovementioned references and withdrawal of the rejection is respectively requested.

Claim 14 stands rejected under 35 U.S.C. §103 (a) as allegedly unpatentable over Chang, et al. (U.S. Patent No. 4,849,224) in view of Jain, et al. (U.S. Patent No. 5,780,050), Patchett, et al. (U.S. Patent No. 6,043,026) and Ke, et al. (*Endocrinology* **139** (4): 2068-2076 (1998)).

Chang, et al. is cited for disclosing a device for the administration of an active agent containing the following elements: a) a backing layer; b) an agent permeable membrane; c) a reservoir containing an active agent; d) a peal seal; e) a heat seal; f) an adhesive overlay; and g) a removable release liner in which the adhesive layers are on the periphery of the device so as not to degrade the components of the reservoir. The Office admitted that Chang, et al. does not disclose the nature of the active agent, but that the use of steroids such as estradiol, would have been obvious.

The Office alleged that Jain, et al. discloses a transdermal formulation comprising a liquid drug reservoir, an adhesive solvent/water based pressure sensitive matrix and a permeation enhancer. Jain, et al. also allegedly discloses the formulation comprising ethanol and glycerol monooleate as possible solvents and penetration enhancers. Jain, et al. further allegedly suggests the use of sex hormones as the active ingredient and that these sex hormones are used to influence various physiological functions.

Patchett, et al. is cited for disclosing a combination therapy for the prevention and treatment of osteoporosis comprised of a compound containing estrogen receptor modulators,

one of which may be lasofoxifene (also known as CP-336156). Patchett, et al. also is alleged to suggest that the compound above can be formulated into a topical solution and that this topical solution can be formulated into a transdermal solution. Ke, et al. is cited for disclosing that lasofoxifene can be used as an estrogen steroid substitute in hormone replacement therapy.

It is the Office's position that one of ordinary skill in the art would have been motivated to combine these teachings to deliver the formulation to the patient without degrading the components of the reservoir. Additionally, the Office alleged that it would have been obvious to one of ordinary skill in the art to combine the device disclosed by Chang, et al. with the formulation disclosed by Jain, et al. and Patchett, et al. to obtain the allegedly expected result of a device to deliver a formulation that would be helpful in the prevention and treatment of estrogen deficiency disorders. Applicants respectfully traverse.

Claim 14 recites a device comprised of a) a backing layer defining an upper portion of a reservoir and extending to the periphery of a peel seal disk: b) an active agent-permeable membrane extending to the periphery of the peel seal disk and the backing layer; c) the reservoir therebetween that contains the formulation of claim 1 (includes an effective amount of lasofoxifene); d) the peel seal disc; e) a heat seal; f) an adhesive overlay that extends beyond the periphery of the peel seal disc; and g) a removable release liner.

Applicants respectfully disagree with the Office. Chang, et al. discloses a device for the administration of an active agent containing at least two heat seals and that this device is important when one or more of the components of the active agent formulation is incompatible with available adhesives that are useful for removably attaching elements to the skin or mucosa. In contrast, the invention of claim 14 requires that "[s]uch adhesives must be physically and chemically compatible with lasofoxifene and optionally the enhancer, and with any carriers and/or vehicles or other additives incorporated into the drug/enhancer composition." *See* specification at page 7, line 30 to page 8, line 1. Therefore the device in claim 14 differs from that disclosed in Chang, et al. in that it requires physical and chemical compatibility of the adhesives with the lasofoxifene composition. There is nothing in the teaching of Patchett, et al., Jain, et al. or Ke, et al. which when combined with Chang, et al. would lead one of ordinary skill

in the art to combine these teachings into a device for transdermal formulation as claimed by Applicants.

Claims 18 and 19 stand rejected under 35 U.S.C. §103 (a) as allegedly unpatentable over Chang, et al. (U.S. Patent No. 4,849,224) in view of Jain, et al. (U.S. Patent No. 5,780,050), Patchett, et al. (U.S. Patent No. 6,043,026), Venkateshwaran, et al. (U.S. Patent No. 5,912,009) and Ke, et al. (*Endocrinology* **139** (4): 2068-2076 (1998)).

Chang, et al. is alleged to teach as summarized above. Jain, et al. is cited for disclosing a transdermal formulation comprising a liquid drug reservoir, an adhesive solvent/water based pressure sensitive matrix and a permeation enhancer such as ethanol and glycerol monooleate. The Office also alleged that Jain, et al. discloses the use of sex hormones as the active ingredient to influence various physiological functions. Patchett, et al. is cited for disclosing a combination therapy for the prevention and treatment of osteoporosis comprised of a compound containing estrogen receptor modulators, one of which allegedly may be lasofoxifene (also known as CP-336156 *see* Ke, et al.). The Office stated that Patchett, et al. suggests that the compound above can be formulated into a topical solution which can be further formulated into a transdermal solution.

The Office opined that Venkateshwaran, et al. teaches a transdermal formulation where a hydroalcoholic gel is created comprising glycerin, water, enhancer and a drug, that may be brought into contact with the skin and is held in place by a type of adhesive. The Office further admitted that Venkateshwaran, et al. does not teach the inclusion of lasofoxifene in the formulation, but nevertheless suggests that the drug can be any number of compounds suitable for topical and transdermal administration including hormones.

The Office alleged that it would have been obvious to one of ordinary skill in the art to combine these teachings under suggestions of the art in order to obtain the allegedly expected result of a device to deliver a formulation that would be helpful in the prevention and treatment of estrogen deficiency disorders. Applicants respectfully traverse.

Claims 18 and 19 recite a method for treating or preventing a disorder associated with estrogen deficiency or disregulation comprising contacting an application or dermal situs of the subject with the device of claim 14.

Chang, et al. discloses a device for the administration of an active agent one or more components are when "one or more of the components of the active agent formulation is incompatible with available adhesives that are useful for removably attaching elements to the skin or mucosa." (Col. 3, lines 53 to 64). In contrast, Applicants' device utilizes adhesives that physically and chemically compatible with lasofoxifene and optionally the enhancer, and with any carriers and/or vehicles or other additives incorporated into the drug/enhancer composition. *See* specification at page 7, line 30 to page 8, line 1. Therefore Chang, et al. is directed to the solution of a problem not present in the devices of the subject invention. There is nothing in the teaching of Venkateshwaran, et al., Patchett, et al., Jain, et al. or Ke, et al. which when combined with Chang, et al. would lead one of ordinary skill in the art to combine these teachings to arrive at the claimed invention.

Additionally, Applicants respectfully disagree that it would have been obvious to one of ordinary skill in the art to combine the device disclosed by Chang, et al. with the formulation disclosed by Jain, et al. Patchett, et al., Ke, et al. and the method of use disclosed by Venkateshwaran, et al. (application to afflicted situs) to obtain the allegedly expected result of a device to deliver a formulation that would be helpful in the prevention and treatment of estrogen deficiency disorders. The active agent disclosed by Patchett, et al. is actually comprised of two separate active ingredients: 1) an estrogen receptor modulator and 2) a growth hormone secretatogogue for use in the treatment or prevention of diseases involving bone resorption. *See* Abstract and claim 1. Additionally, Jain, et al. teaches a stabilized patch device for transdermal drug delivery of steroid drugs which contain a 3-keto-4-en functional group. *See* abstract; column 1, lines 12 through 14; claim 2. Applicants' invention may, in one embodiment, be comprised of a transdermal delivery system containing only lasofoxifene as the active ingredient. Lasofoxifene is not a sex hormone or steroid drug which contains a 3-keto-4-en functional group nor a growth hormone secretatogue. Chang, et al. in view of Venkateshwaran, et al., Jain, et al., Patchett, et al. and Ke, et al. does not teach the application of its patch device for the transdermal delivery of lasofoxifene. Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 103 (a).

Prior Art

Applicants acknowledge the Office's assertion that prior art made of record and not relied upon is considered by the Office to be pertinent to Applicants' disclosure.

III. CONCLUSION

If a telephone interview would advance prosecution of the subject application, the Examiner is invited to telephone the undersigned at the number provided below.

In the unlikely event that the transmittal letter is separated from this document and/or the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-1189**, referencing billing reference **23913-7001.** However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Date: June 26, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 15 has been amended as follows:

15. (Amended) A method for treating or preventing a disorder associated with estrogen deficiency or [disdregulation] disregulation in a subject comprising contacting an application situs of the subject with an effective pharmaceutical formulation of claim 1.